Building on our current treatments | is precision medicine the future for cholangiocarcinoma?

Juan W Valle
University of Manchester / The Christie
Manchester, UK
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<table>
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<th>Disclosures</th>
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<tr>
<td><strong>Travel Grant</strong></td>
<td>Celgene; NuCana; Pfizer</td>
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Every patient is an individual

Things we (as doctors) need to know:

1. **About the cancer itself:**
   a. What type of biliary tract cancer
   b. What “stage” is the cancer at?
   c. What treatment has already been given?
   d. Do we know about the molecular profile?
   e. Is there a clinical trial option?

2. **About the patient**
   a. Level of fitness (“performance status”)
   b. Other health problems
   c. Other medication
   d. Preferences

3. **What are we trying to achieve?**
What type of cholangiocarcinoma?

This question is about ANATOMY (part of the body) - “Where has the cancer started?”

![Diagram showing the anatomy of the liver and bile ducts]

- Inside the liver
- Outside the liver

Need a biopsy for confirmation
What stage is the cancer at?

Early  Locally advanced  metastatic

How do we establish this?
- CT scan
- MRI scan
- Maybe a PET scan
About the patient…

Level of fitness ("performance status")

Score
PS 0 – well and no symptoms at all
PS 1 – well with some symptoms
PS 2 – needing help, up for more than ½ day
PS 3 – in bed more than ½ the day
PS 4 – very unwell, needing all care

Well enough for treatment
Borderline
Not well enough for treatment

Other health problems

Other medication

Preferences
Building on our current treatments
What stage is the cancer at?

Early

Locally advanced

metastatic

Surgery…
- Performed in specialist centres
- Aiming to remove all of the cancer
- Also removing lymph nodes next to the cancer

…followed by 6-month course of oral chemotherapy (capecitabine)
- To “mop up” any remaining cancer cells
- Reduces the chance of the cancer returning
- Improves survival
What stage is the cancer at?

- Early
- Locally advanced
- Metastatic

- Surgery is not possible
- Treatment is the same (chemotherapy) as for metastatic disease (more advanced)
- It may be possible to give additional local treatment (e.g. radiotherapy)

Occasionally, if the disease responds well to treatment (shrinks), it may be possible to do surgery.
What stage is the cancer at?

- Early
- Locally advanced
- Metastatic

Unfortunately, this is the majority of patients.
Current treatment is chemotherapy.
Treatment usually for 6 months.
Monitoring CT scans, blood tests, side-effects and quality of life.

First-line:
- PS 0-1: cisplatin and gemcitabine
- PS2: gemcitabine alone
What stage is the cancer at?

- Early
- Locally advanced
- Metastatic

Unfortunately, this is the majority of patients
- Current treatment is chemotherapy
- Treatment usually for 6 months
- Monitoring CT scans, blood tests, side-effects and quality of life

**Second line:**
- PS 0-1: oxaliplatin and 5-fluorouracil *
  (*also known as FOLFOX or OxMdG)
Building on our current treatments
What approaches are being tried?

• Intensifying chemotherapy (3-drug combinations)
• New drugs (like NUC-1031, Etoposide Toniribate (EDO S7.1))
• New modalities
  – Proton beam
  – HAI
  – Radioembolisation
• Molecularly-targeted therapy
What is precision medicine?

Here all patients are treated the same...
- Some respond to treatment
- Others do not

Here, patients are treated according to their molecular profile, increasing the chances of benefit.
What is precision medicine?

Here all patients are treated the same...
- Some respond to treatment
- Others do not

“fingerprinting” of DNA, RNA, proteins on TUMOUR BIOPSY

Here, patients are treated according to their molecular profile, increasing the chances of benefit
Learning a lot about the genetics of CCA

Figure from Valle et al Cancer Discov 2017;7(9):943-962
From anatomical to molecular subgroups

Figure from Lamarca A, et al. J Hepatol. 2020
Molecular profiling and targeted therapies

At the moment, these therapies *only* apply to patients with advanced disease.
Looking for FGFR2 fusions

FIGHT-202 study
Each bar represents 1 patient

Overall response rate 35.5%
Disease control rate 82.2%
Median Duration of Response 7.5 months

Applies to about 10-15% of patients with iCCA

Figure from Lamarca A, et al. J Hepatol. 2020

Abou Alfa et al. Lancet Oncol. 2020
First targeted treatment approved...
in the USA

@US_FDA has approved @Incyte's Pemazyre (pemigatinib) for the treatment of advanced cholangiocarcinoma, but this targeted therapy is not available in the UK or Europe. To find out why, see: ammf.org.uk/2020/04/24/fda...

#bileductcancer #cancer
There are many FGFR2-targeted agents

- Infigratinib (BJG398) Novartis/QED
- Pemigatinib (INCB054828) Incyte
- Derazantinib (ARQ 087) Arqule/Basilea
- Futibatinib (TAS-120) Taiho

References:
1. Javle et al ESMO 2018 abstr #LBA28
2. Hollebecque et al ESMO 2018 756P
4. Meric-Bernstam et al ESMO-GI 2018 abstr O-001
Looking for mutations in IDH1

ClarIDHy study
Each bar represents 1 patient

Ivosidenib delayed the cancer from getting worse by 63%
Patients were allowed to cross over
Patients receiving ivosidenib seem to live longer, but mature results are awaited

Figure from Lamarca A, et al. J Hepatol. 2020
Applies to about 10-15% of patients with iCCA

Abou Alfa et al. Lancet Oncol. 2020
Looking for NTRK fusions
neurotrophic receptor tyrosine kinase

- **Nov 2018** | FDA grants accelerated approval to larotrectinib for patients with solid tumours that have a NTRK gene fusion
- **STARTRK-2 study (entrectenib) recruiting** [NCT02568267]

Looking for mismatch repair deficiency

May 2017 | FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

Relevant to ~2.5% of cholangiocarcinoma patients

1 Le et al NEJM 2015; 372(26):2509-20

2 https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm
Looking for mismatch repair deficiency
### Upper gastrointestinal cancers (oesophageal, gastric, small bowel, biliary tract, pancreatic)

- Option to give nivolumab instead of chemotherapy for microsatellite instability-high tumours to reduce toxicity of treatment **[added 3 August 2020]**

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NHS England interim treatment options during the COVID-19 pandemic (last updated 22 October 2020)
What about a “liquid biopsy”

“Precision Medicine” is not possible for ALL Patients

- Reason #1: Quality tissue sample not always available
  - Cytology-based diagnosis
  - Failed tissue samples

- Reason #2: Targetable finding ~40% of patients
  - ~60%: not suitable for targeted therapies

We will still need new chemotherapy options

Lamarca et al. JCM. 2020.
Getting involved in clinical trials

Current Cholangiocarcinoma Trials

Listed here are the clinical trials for those with cholangiocarcinoma (bile duct cancer) or gall bladder cancer, currently open and recruiting in the UK.

Wherever possible links for further information have been included to follow up for more information and to check eligibility. Each trial has specific eligibility criteria, so if you are interested in taking part in one, please discuss with those running the trial (contact details are given where possible) and/or your consultant.

Please note it is not appropriate for AMMF to
Every patient is an individual

- Our understanding of the biology (what makes the cancer tick) is improving
- In early-stage disease surgery followed by chemotherapy gives the best chance of cure
- Molecular profiling is increasingly important as it can lead to new treatment options
- We still have the other pillars of therapy: chemotherapy and radiotherapy
- Clinical research is accelerating and new treatments emerging
- The role of immunotherapy is being extensively evaluated
Acknowledgements